ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tolvaptan Accord 7.5 mg tablets
Tolvaptan Accord 15 mg tablets
Tolvaptan Accord 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tolvaptan Accord 7.5 mg tablets

Each tablet contains 7.5 mg tolvaptan.
Excipient with known effect
17.5 mg lactose (as monohydrate) per tablet

Tolvaptan Accord 15 mg tablets

Each tablet contains 15 mg tolvaptan.
Excipient with known effect
35 mg lactose (as monohydrate) per tablet

Tolvaptan Accord 30 mg tablets

Each tablet contains 30 mg tolvaptan.
Excipient with known effect
70 mg lactose (as monohydrate) per tablet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Tolvaptan Accord 7.5 mg tablets
Light blue to blue coloured, round, biconvex, uncoated tablets, debossed with "MT" on one side and "18" on other side with approximate dimension of 5.0 mm.

Tolvaptan Accord 15 mg tablets
Light blue to blue coloured, triangle, biconvex, uncoated tablets, debossed with '"MT" on one side and "7" on other side with approximate dimension of 6.7 x 6.3 x 3.3 mm.

Tolvaptan Accord 30 mg tablets
Light blue to blue coloured, round, biconvex, uncoated tablets, debossed with "MT" on one side and "8" on other side with approximate dimension of 8.1 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tolvaptan is indicated in adults for the treatment of hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

4.2 Posology and method of administration

Due to the need for a dose titration phase with close monitoring of serum sodium and volume status (see section 4.4), treatment with tolvaptan has to be initiated in hospital.

Posology

Tolvaptan has to be initiated at a dose of 15 mg once daily. The dose may be increased to a maximum of 60 mg once daily as tolerated to achieve the desired level of serum sodium.

For patients at risk of overly rapid correction of sodium e.g., patients with oncological conditions, very low baseline serum sodium, taking diuretics, or taking sodium supplementation a dose of 7.5 mg should be considered (see section 4.4).

During titration, patients must be monitored for serum sodium and volume status (see section 4.4). In case of inadequate improvement in serum sodium levels, other treatment options have to be considered, either in place of or in addition to tolvaptan. Use of tolvaptan in combination with other options may increase the risk of overly rapid correction of serum sodium (see sections 4.4 and 4.5). For patients with an appropriate increase in serum sodium, the underlying disease and serum sodium levels must be monitored at regular intervals to evaluate further need of tolvaptan treatment. In the setting of hyponatremia, the treatment duration is determined by the underlying disease and its treatment. Tolvaptan treatment is expected to last until the underlying disease is adequately treated or until such time that hyponatremia is no longer a clinical issue.
Tolvaptan must not be taken with grapefruit juice (see section 4.5).

Special populations

Renal impairment
Tolvaptan is contraindicated in anuric patients (see section 4.3).
Tolvaptan has not been studied in patients with severe renal failure. The efficacy and safety in this population is not well established.
Based on the data available, no dose adjustment is required in those with mild to moderate renal impairment.

Hepatic impairment
No information is available in patients with severe hepatic impairment (Child-Pugh class C). In these patients dosing has to be managed cautiously and electrolytes and volume status must be monitored (see section 4.4). No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B).

Elderly
No dose adjustment is needed in elderly patients.

Paediatric population
The safety and efficacy of tolvaptan in children and adolescents under the age of 18 years have not yet been established. Tolvaptan is not recommended in the paediatric age group.

Method of administration

Oral use.

Administration preferably in the morning, without regard to meals. Tablets must be swallowed without chewing with a glass of water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to benzazepine or benzazepine derivatives (see section 4.4)
- Anuria
- Volume depletion
- Hypovolemic hyponatremia
- Hypernatremia
- Patients who cannot perceive thirst
- Pregnancy (see section 4.6)
- Breast-feeding (see section 4.6)

4.4 Special warnings and precautions for use

Urgent need to raise serum sodium acutely

Tolvaptan has not been studied in a setting of urgent need to raise serum sodium acutely. For such patients, alternative treatment has to be considered.

Access to water

Tolvaptan may cause adverse reactions related to water loss such as thirst, dry mouth and dehydration (see section 4.8). Therefore, patients must have access to water and be able to drink sufficient amounts of water. If fluid restricted patients are treated with tolvaptan, extra caution has to be exercised to ensure that patients do not become overly dehydrated.

Dehydration

Volume status must be monitored in patients taking tolvaptan because treatment with tolvaptan may result in severe dehydration, which constitutes a risk factor for renal dysfunction. If dehydration becomes evident, take appropriate action which may include the need to interrupt or reduce the dose of tolvaptan and increase fluid intake.

Urinary outflow obstruction

Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention.

Fluid and electrolyte balance

Fluid and electrolyte status has to be monitored in all patients and particularly in those with renal and hepatic impairment. Administration of tolvaptan may cause too rapid increases in serum sodium ($\geqslant$ 12 mmol/L per 24 hours, please see below); therefore, monitoring of serum sodium in all patients must start no later than 4 to 6 hours after treatment initiation. During the first 1 to 2 days and until the tolvaptan dose is stabilised serum sodium and volume status must be monitored at least every 6 hours.

Too rapid correction of serum sodium

Patients with very low baseline serum sodium concentrations may be at greater risk for too rapid correction of serum sodium.
Too rapid correction of hyponatremia (increase $\geqslant$ 12 mmol/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death. Therefore, after initiation of treatment, patients have to be closely monitored for serum sodium and volume status (see above).
In order to minimise the risk of too rapid correction of hyponatremia the increase of serum sodium should be less than 10 mmol/L/24 hours to 12 mmol/L/24 hours and less than 18 mmol/L/48 hours. Therefore, more precautionary limits apply during the early treatment phase.

If sodium correction exceeds 6 mmol/L during the first 6 hours of administration or 8 mmol/L during the first 6 to 12 hours, respectively, the possibility that serum sodium correction may be overly rapid should be considered. These patients should be monitored more frequently regarding their serum sodium and administration of hypotonic fluid is recommended. In case serum sodium increases $\geqslant$ 12 mmol/L within 24 hours or $\geqslant$ 18 mmol/L within 48 hours, tolvaptan treatment is to be interrupted or discontinued followed by administration of hypotonic fluid.
In patients at higher risk of demyelination syndromes, for example those with hypoxia, alcoholism or malnutrition, the appropriate rate of sodium correction may be lower than that in patients without risk factors; these patients should be very carefully managed.

Patients who received other treatment for hyponatremia or medicinal products which increase serum sodium concentration (see section 4.5) prior to initiation of treatment with tolvaptan must be managed very cautiously. These patients may be at higher risk for developing rapid correction of serum sodium during the first 1 to 2 days of treatment due to potential additive effects.
Co-administration of tolvaptan with other treatments for hyponatremia, and medicinal products that increase serum sodium concentration, is not recommended during initial treatment or for other patients with very low baseline serum sodium concentrations (see section 4.5).

Diabetes mellitus

Diabetic patients with an elevated glucose concentration (e.g., in excess of 300 mg/dL) may present with pseudo-hyponatremia. This condition should be excluded prior and during treatment with tolvaptan.
Tolvaptan may cause hyperglycemia (see section 4.8). Therefore, diabetic patients treated with tolvaptan should be managed cautiously. In particular this applies to patients with inadequately controlled type II diabetes.

Idiosyncratic hepatic toxicity

Liver injury induced by tolvaptan was observed in clinical trials investigating a different indication (autosomal dominant polycystic kidney disease [ADPKD]) with long-term use of tolvaptan at higher doses than for the approved indication (see section 4.8).

In post-marketing experience with tolvaptan in ADPKD, acute liver failure requiring liver transplantation has been reported (see section 4.8).

In these clinical trials, clinically significant increases (greater than 3 × Upper Limit of Normal [ULN]) in serum alanine aminotransferase (ALT), along with clinically significant increases (greater than 2 × ULN) in serum total bilirubin were observed in 3 patients treated with tolvaptan. In addition, an increased incidence of significant elevations of ALT was observed in patients treated with tolvaptan [4.4 % (42/958)] compared to those receiving placebo [1.0 % (5/484)]. Elevation (> 3 × ULN) of serum aspartate aminotransferase (AST) was observed in 3.1 % (30/958) of patients on tolvaptan and 0.8 % (4/484) patients on placebo. Most of the liver enzyme abnormalities were observed during the first 18 months of treatment. The elevations gradually improved after discontinuation of tolvaptan. These findings may suggest that tolvaptan has the potential to cause irreversible and potentially fatal liver injury.

In a post-authorisation safety study of tolvaptan in hyponatremia secondary to SIADH, several cases of hepatic disorders and elevated transaminases were observed (see section 4.8).

Liver function tests must be promptly performed in patients taking tolvaptan who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. If liver injury is suspected, tolvaptan must be promptly discontinued, appropriate treatment has to be instituted, and investigations have to be performed to determine the probable cause. Tolvaptan must not be re-initiated in patients unless the cause for the observed liver injury is definitively established to be unrelated to treatment with tolvaptan.

Anaphylaxis

In post-marketing experience, anaphylaxis (including anaphylactic shock and generalised rash) has been reported very rarely following administration of tolvaptan. Patients have to be carefully monitored during treatment. Patients with known hypersensitivity reactions to benzazepine or benzazepine derivatives (e.g., benazepril, conivaptan, fenoldopam mesylate or mirtazapine) may be at risk for hypersensitivity reaction to tolvaptan (see section 4.3 Contraindications).

If an anaphylactic reaction or other serious allergic reactions occur, administration of tolvaptan must be discontinued immediately and appropriate therapy initiated. Since hypersensitivity is a contraindication (see section 4.3) treatment must never be restarted after an anaphylactic reaction or other serious allergic reactions.

Lactose

Tolvaptan contains lactose as an excipient. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration with other treatments for hyponatremia and medicinal products that increase serum sodium concentration

There is no experience from controlled clinical trials with concomitant use of tolvaptan and other treatments for hyponatremia such as hypertonic sodium chloride solution, oral sodium formulations, and medicinal products that increase serum sodium concentration. Medicinal products with high sodium content such as effervescent analgesic preparations and certain sodium containing treatments for dyspepsia may also increase serum sodium concentration. Concomitant use of tolvaptan with other treatments for hyponatremia or other medicinal products that increase serum sodium concentration may result in a higher risk for developing rapid correction of serum sodium (see section 4.4) and is therefore not recommended during initial treatment or for other patients with very low baseline serum sodium concentrations where rapid correction may represent a risk for osmotic demyelination (see section 4.4).

Effect of other medicinal products on the pharmacokinetics of tolvaptan

CYP3A4 inhibitors

Tolvaptan plasma concentrations have been increased by up to 5.4-fold area under time-concentration curve (AUC) after the administration of strong CYP3A4 inhibitors. Caution should be exercised in co-administering CYP3A4 inhibitors (e.g. ketoconazole, macrolide antibiotics, diltiazem) with tolvaptan. Co-administration of grapefruit juice and tolvaptan resulted in a 1.8-fold increase in exposure to tolvaptan. Patients taking tolvaptan should avoid ingesting grapefruit juice.

CYP3A4 inducers

Tolvaptan plasma concentrations have been decreased by up to 87 % (AUC) after the administration of CYP3A4 inducers. Caution has to be exercised in co-administering CYP3A4 inducers (e.g. rifampicin, barbiturates and St. John’s wort) with tolvaptan.

Effect of tolvaptan on the pharmacokinetics of other products

CYP3A4 substrates

In healthy subjects, tolvaptan, a CYP3A4 substrate, had no effect on the plasma concentrations of some other CYP3A4 substrates (e.g., warfarin or amiodarone). Tolvaptan increased plasma levels of

lovastatin by 1.3-fold to 1.5-fold. Even though this increase has no clinical relevance, it indicates tolvaptan can potentially increase exposure to CYP3A4 substrates.

Transporter substrates

P-glycoprotein substrates
In-vitro studies indicate that tolvaptan is a substrate and competitive inhibitor of P-glycoprotein (P-gp). Steady state digoxin concentrations were increased (1.3-fold in maximum observed plasma concentration [C_{max}] and 1.2-fold in area under the plasma concentration-time curve over the dosing interval [AUC_{τ}]) when co-administered with multiple once daily 60 mg doses of tolvaptan. Patients receiving digoxin or other narrow therapeutic index P-gp substrates (e.g., dabigatran etexilate) must therefore be managed cautiously and evaluated for excessive effects when treated with tolvaptan.

BCRP and OCT1
Co-administration of tolvaptan (90 mg) with rosuvastatin (5 mg), a BCRP substrate, increased rosuvastatin C_{max} and AUC_t of 54 % and 69 %, respectively. If BCRP substrates (e.g., sulfasalazine) are co-administered with tolvaptan, patients must be managed cautiously and evaluated for excessive effects of these medicinal products.
If OCT1 substrates (e.g., metformin) are co-administered with tolvaptan, patients must be managed cautiously and evaluated for excessive effects of these medicinal products.

Diuretics

While there does not appear to be a synergistic or additive effect of concomitant use of tolvaptan with loop and thiazide diuretics, each class of agent has the potential to lead to severe dehydration, which constitutes a risk factor for renal dysfunction. If dehydration or renal dysfunction becomes evident, take appropriate action which may include the need to interrupt or reduce doses of tolvaptan and/or diuretics, increase fluid intake, evaluate and address other potential causes of renal dysfunction or dehydration.

Co-administration with vasopressin analogues

In addition to its renal aquaretic effect, tolvaptan is capable of blocking vascular vasopressin V2-receptors involved in the release of coagulation factors (e.g., von Willebrand factor) from endothelial cells. Therefore, the effect of vasopressin analogues such as desmopressin may be attenuated in patients using such analogues to prevent or control bleeding when co-administered with tolvaptan.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of tolvaptan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Tolvaptan is contraindicated during pregnancy (see section 4.3). Women of childbearing potential have to use effective contraception during tolvaptan treatment.

Breast-feeding

It is unknown whether tolvaptan is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of tolvaptan in breast milk (for details see 5.3). The potential risk for humans is unknown. Tolvaptan is contraindicated during breast-feeding (see section 4.3).

Fertility

Studies in animals showed effects on fertility (see section 5.3). The potential risk for humans is unknown.

4.7 Effects on ability to drive and use machines

Tolvaptan has no or negligible influence on the ability to drive or use machines. However, when driving or using machines it should be taken into account that occasionally dizziness, asthenia or syncope may occur.

4.8 Undesirable effects

Summary of the safety profile

The adverse reaction profile of tolvaptan in SIADH is based on a clinical trials database of 3 294 tolvaptan-treated patients and is consistent with the pharmacology of the active substance. The pharmaco-dynamically predictable and most commonly reported adverse reactions are thirst, dry mouth and pollakiuria occurring in approximately 18 %, 9 % and 6 % of patients.

Tabulated list of adverse reactions

The frequencies of the adverse reactions from clinical trials correspond with very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse reactions is qualified as "not known".

System Organ Class	**Frequency**			
	Very common	Common	Uncommon	Not known
Immune system disorders				Anaphylactic shock, Generalised rash
Metabolism and nutrition disorders		Polydipsia, Dehydration, Hyperkalemia, Hyperglycemia, Hypoglycemia[1], Hypernatremia[1], Hyperuricemia[1], Decreased appetite		
Nervous system disorders		Syncope[1], Headache[1], Dizziness[1]	Dysgeusia	
Vascular disorders		Orthostatic hypotension		
Gastrointestinal disorders	Nausea	Constipation, Diarrhoea[1], Dry mouth		

System Organ Class	Frequency			
	Very common	Common	Uncommon	Not known
Skin and subcutaneous tissue disorders		Ecchymosis, Pruritus	Pruritic rash[1]	
Renal and urinary disorders		Pollakiuria, Polyuria	Renal impairment	
General disorders and administration site conditions	Thirst	Asthenia, Pyrexia, Malaise[1]		
Hepatobiliary disorders				Hepatic disorders[2] Acute hepatic failure[3]
Investigations		Blood urine present[1], Alanine aminotransferase increased (see section 4.4)[1], Aspartate aminotransferase increased (see section 4.4)[1], Blood creatinine increased.	Bilirubin increased (see section 4.4)[1]	Elevated transaminases[2]
Surgical and medical procedures	Rapid correction of hyponatremia, sometimes leading to neurological symptoms			

[1] observed in clinical trials investigating other indications
[2] from post-authorisation safety study in hyponatremia secondary to SIADH
[3] observed in post-marketing with tolvaptan in ADPKD. Liver transplantation was necessary.

Description of selected adverse reactions

Rapid correction of hyponatremia
In a post-authorisation safety study of tolvaptan in hyponatremia secondary to SIADH, including a high proportion of patients with tumours (especially small cell lung cancer), patients with low baseline serum sodium as well as patients with concomitant use of diuretics and/or sodium chloride solution the incidence of rapid correction of hyponatremia was found to be higher than in clinical trials.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Single doses up to 480 mg and multiple doses up to 300 mg per day for 5 days have been well tolerated in clinical trials in healthy volunteers. There is no specific antidote for tolvaptan intoxication. The signs and symptoms of an acute overdose can be anticipated to be those of excessive

pharmacologic effect: a rise in serum sodium concentration, polyuria, thirst and dehydration/hypovolemia (profuse and prolonged aquaresis).

In patients with suspected tolvaptan overdose, assessment of vital signs, electrolyte concentrations, ECG and fluid status is recommended. Appropriate replacement of water and/or electrolytes must continue until aquaresis abates. Dialysis may not be effective in removing tolvaptan because of its high binding affinity for human plasma protein (> 98 %).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diuretics, vasopressin antagonists, ATC code: C03XA01

Mechanism of action

Tolvaptan is a selective vasopressin V2-receptor antagonist that specifically blocks the binding of arginine vasopressin (AVP) at the V2-receptor of the distal portions of the nephron. Tolvaptan affinity for the human V2-receptor is 1.8-times that of native AVP.

In healthy adult subjects, oral administration of 7.5 mg to 120 mg doses of tolvaptan produced an increase in urine excretion rate within 2 hours of dosing. Following single oral doses of 7.5 mg to 60 mg, 24-hour urine volume increased dose dependently with daily volumes ranging from 3 to 9 litres. For all doses, urine excretion rates returned to baseline levels after 24 hours. For single doses 60 mg to 480 mg, a mean of about 7 litres was excreted during 0 to 12 hours, independent of dose. Markedly higher doses of tolvaptan produce more sustained responses without affecting the magnitude of excretion, as active concentrations of tolvaptan are present for longer periods of time.

Clinical efficacy and safety

Hyponatremia
In 2 pivotal, double-blind, placebo-controlled, clinical trials, a total of 424 patients with euvolemic or hypervolemic hyponatremia (serum sodium < 135 mEq/L) due to a variety of underlying causes (heart failure [HF], liver cirrhosis, SIADH and others) were treated for 30 days with tolvaptan (n = 216) or placebo (n = 208) at an initial dose of 15 mg/day. The dose could be increased to 30 mg/day and 60 mg/day depending on response using a 3-day titration scheme. The mean serum sodium concentration at trial entry was 129 mEq/L (range 114 mEq/L to 136 mEq/L).

The primary endpoint for these trials was the average daily AUC for change in serum sodium from baseline to Day 4 and baseline to Day 30. Tolvaptan was superior to placebo ($p < 0.0001$) for both periods in both studies. This effect was seen in all patients, the severe (serum sodium: < 130 mEq/L) and mild (serum sodium: 130 mEq/L to < 135 mEq/L) subsets and for all disease aetiology subsets (e.g., HF, cirrhosis, SIADH/other). At 7 days after discontinuing treatment, sodium values decreased to levels of placebo treated patients.

Following 3 days of treatment, the pooled analysis of the two trials revealed 5-fold more tolvaptan than placebo patients achieved normalisation of serum sodium concentrations (49 % *vs.* 11 %). This effect continued as on Day 30, when more tolvaptan than placebo patients still had normal concentrations (60 % *vs*. 27 %). These responses were seen in patients independent of the underlying disease. The results of self-assessed health status using the SF-12 Health Survey for the mental scores showed statistically significant and clinically relevant improvements for tolvaptan treatment compared to placebo.

Data on the long-term safety and efficacy of tolvaptan were assessed for up to 106 weeks in a clinical trial in patients (any aetiology) who had previously completed one of the pivotal hyponatremia trials. A total of 111 patients started tolvaptan treatment in an open-label, extension trial, regardless of their

previous randomisation. Improvements in serum sodium levels were observed as early as the first day after dosing and continued for on-treatment assessments up to Week 106. When treatment was discontinued, serum sodium concentrations decreased to approximately baseline values, despite the reinstatement of standard care therapy.

In a pilot, randomised (1:1:1), double-blind trial in 30 patients with hyponatremia secondary to SIADH, the pharmacodynamics of tolvaptan following single doses of 3.75 mg, 7.5 mg and 15 mg were assessed. Results were highly variable with large overlap between dose groups; changes were not significantly correlated with tolvaptan exposure. Mean maximal changes in serum sodium were highest following the 15 mg dose (7.9 mmol/L) but median maximal changes were highest for the 7.5 mg dose (6.0 mmol/L). Individual maximal increases in serum sodium were negatively correlated with fluid balance; mean change in fluid balance showed a dose dependent decrease. Mean change from baseline in cumulative urine volume and urine excretion rates was 2-fold higher for the 15 mg dose compared to the 7.5 mg and 3.75 mg doses, which showed similar responses.

Heart failure
EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) was a long-term outcome, double-blind, controlled clinical trial in patients hospitalised with worsening HF and signs and symptoms of volume overload. In the long-term outcome trial, a total of 2 072 patients received 30 mg tolvaptan with standard of care (SC) and 2 061 received placebo with SC. The primary objective of the study was to compare the effects of tolvaptan + SC with placebo + SC on the time to all-cause mortality and on the time to first occurrence of cardiovascular (CV) mortality or hospitalisation for HF. Tolvaptan treatment had no statistically significant favourable or unfavourable effects on overall survival or the combined endpoint of CV mortality or HF hospitalisation, and did not provide convincing evidence for clinically relevant benefit.

The European Medicines Agency has deferred the obligation to submit the results of studies with tolvaptan in one or more subsets of the paediatric population in treatment of dilutional hyponatremia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

After oral administration, tolvaptan is rapidly absorbed with peak plasma concentrations occurring about 2 hours after dosing. The absolute bioavailability of tolvaptan is about 56 %. Co-administration of a 60 mg dose with a high-fat meal increases peak concentrations 1.4-fold with no change in AUC and no change in urine output. Following single oral doses of ≥ 300 mg, peak plasma concentrations appear to plateau, possibly due to saturation of absorption.

Distribution

Tolvaptan binds reversibly (98 %) to plasma proteins.

Biotransformation

Tolvaptan is extensively metabolised by the liver. Less than 1 % of intact active substance is excreted unchanged in the urine.
In-vitro studies indicate that tolvaptan or its oxobutyric metabolite may have the potential to inhibit OATP1B1, OAT3, BCRP and OCT1 transporters. Administration of rosuvastatin (OATP1B1 substrate) or furosemide (OAT3 substrate) to healthy subjects with elevated oxobutyric acid metabolite (inhibitor of OATP1B1 and OAT3) plasma concentrations did not meaningfully alter the pharmacokinetics of rosuvastatin or furosemide. See also section 4.5.

Elimination

The terminal elimination half-life is about 8 hours and steady-state concentrations of tolvaptan are obtained after the first dose.

Radio-labelled tolvaptan experiments showed that 40 % of the radioactivity was recovered in the urine and 59 % was recovered in the faeces where unchanged tolvaptan accounted for 32 % of radioactivity. Tolvaptan is only a minor component in plasma (3 %).

Linearity

Tolvaptan has linear pharmacokinetics for doses of 7.5 mg to 60 mg.

Pharmacokinetics in special patient groups

Age
Clearance of tolvaptan is not significantly affected by age.

Hepatic impairment
The effect of mildly or moderately impaired hepatic function (Child-Pugh classes A and B) on the pharmacokinetics of tolvaptan was investigated in 87 patients with liver disease of various origins. No clinically significant changes have been seen in clearance for doses ranging from 5 mg to 60 mg. Very limited information is available in patients with severe hepatic impairment (Child-Pugh class C).

In a population pharmacokinetic analysis in patients with hepatic oedema, AUC of tolvaptan in severely (Child-Pugh class C) and mildly or moderately (Child-Pugh classes A and B) hepatic impaired patients were 3.1-times and 2.3-times higher than that in healthy subjects.

Renal impairment
In an analysis on population pharmacokinetics for patients with heart failure, tolvaptan concentrations of patients with mildly (creatinine clearance [C_{cr}] 50 mL/min to 80 mL/min) or moderately (C_{cr} 20 mL/min to 50 mL/min) impaired renal function were not significantly different to tolvaptan concentrations in patients with normal renal function (C_{cr} 80 mL/min to 150 mL/min). The efficacy and safety of tolvaptan in those with a creatinine clearance < 10 mL/min has not been evaluated and is therefore unknown.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential.

Teratogenicity was noted in rabbits given 1 000 mg/kg/day (3.9-times the exposure in humans at the 60 mg dose, based on AUC). No teratogenic effects were seen in rabbits at 300 mg/kg/day (up to 1.9-times the exposure in humans at the 60 mg dose, based on AUC).
In a peri-and post-natal study in rats, delayed ossification and reduced pup bodyweight were seen at the high dose of 1 000 mg/kg/day.
Two fertility studies in rats showed effects on the parental generation (decreased food consumption and body weight gain, salivation), but tolvaptan did not affect reproductive performance in males and there were no effects on the foetuses. In females, abnormal oestrus cycles were seen in both studies. The no observed adverse effects level (NOAEL) for effects on reproduction in females (100 mg/kg/day) was about 6.7-times the exposure in humans at the 60 mg dose, based on AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Magnesium stearate
Croscarmellose sodium
Hydroxypropyl cellulose
Maize starch
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

Tolvaptan Accord 7.5/15/30 mg tablets are available as 7x1, 10x1, 28x1, 30x1 tablet in perforated unit dose PVC/Alu blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est, 6ª Planta,
08039 Barcelona,
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1719/001-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 March 2023.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Accord Healthcare Polska Sp. z.o.o.
ul.Lutomierska 50,
95-200, Pabianice, Poland

Pharmadox Healthcare Limited
KW20A Kordin Industrial Park,
Paola PLA 3000, Malta

Accord Healthcare B.V.
Winthontlaan 200,
3526 KV Utrecht, Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tolvaptan Accord 7.5 mg tablets
tolvaptan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 7.5 mg tolvaptan.

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

7×1 tablet
10×1 tablet
28×1 tablet
30×1 tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est, 6ª Planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1719/001
EU/1/23/1719/002
EU/1/23/1719/003
EU/1/23/1719/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tolvaptan Accord 7.5 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

UNIT DOSE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Tolvaptan Accord 7.5 mg tablets
tolvaptan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tolvaptan Accord 15 mg tablets
tolvaptan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 15 mg tolvaptan.

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

7×1 tablet
10×1 tablet
28×1 tablet
30×1 tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est, 6ª Planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1719/005
EU/1/23/1719/006
EU/1/23/1719/007
EU/1/23/1719/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tolvaptan Accord 15 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

UNIT DOSE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Tolvaptan Accord 15 mg tablets
tolvaptan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tolvaptan Accord 30 mg tablets
tolvaptan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 30 mg tolvaptan.

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

7×1 tablet
10×1 tablet
28×1 tablet
30×1 tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est, 6ª Planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1719/009
EU/1/23/1719/010
EU/1/23/1719/011
EU/1/23/1719/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tolvaptan Accord 30 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

UNIT DOSE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Tolvaptan Accord 30 mg tablets
tolvaptan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tolvaptan Accord 7.5 mg tablets
Tolvaptan Accord 15 mg tablets
Tolvaptan Accord 30 mg tablets
tolvaptan

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tolvaptan Accord is and what it is used for
2. What you need to know before you take Tolvaptan Accord
3. How to take Tolvaptan Accord
4. Possible side effects
5. How to store Tolvaptan Accord
6. Contents of the pack and other information

1. What Tolvaptan Accord is and what it is used for

Tolvaptan Accord, which contains the active substance tolvaptan, belongs to a group of medicines called vasopressin antagonists. Vasopressin is a hormone that helps prevent the loss of water from the body by reducing urine output. Antagonist means that it prevents vasopressin having its effect on water retention. This leads to a reduction in the amount of water in the body by increasing urine production and as a result it increases the level or concentration of sodium in your blood.

Tolvaptan Accord is used to treat low serum sodium levels in adults. You have been prescribed this medicine because you have a lowered sodium level in your blood as a result of a disease called "syndrome of inappropriate antidiuretic hormone secretion" (SIADH) where the kidneys retain too much water. This disease causes an inappropriate production of the hormone vasopressin which has caused the sodium levels in your blood to get too low (hyponatremia). That can lead to difficulties in concentration and memory, or in keeping your balance.

2. What you need to know before you take Tolvaptan Accord

Do not take Tolvaptan Accord
- if you are allergic to tolvaptan or any of the other ingredients of this medicine (listed in section 6) or if you are allergic to benzazepine or benzazepine derivatives (e.g., benazepril, conivaptan, fenoldopam mesylate or mirtazapine)
- if your kidneys do not work (no urine production)
- if you have a condition which increases the salt in your blood ("hypernatremia")
- if you have a condition which is associated with a very low blood volume
- if you do not realise when you are thirsty
- if you are pregnant
- if you are breast-feeding.

Warnings and precautions

Talk to your doctor or pharmacist before taking Tolvaptan Accord:
- if you cannot drink enough water or if you are fluid restricted
- if you have difficulties in urination or have an enlarged prostate
- if you suffer from liver disease
- if you had an allergic reaction in the past to benzazepine, tolvaptan or other benzazepine derivatives (e.g., benazepril, conivaptan, fenoldopam mesylate or mirtazapine), or to any of the other ingredients of this medicine (listed in section 6).
- if you suffer from a kidney disease called autosomal dominant polycystic kidney disease (ADPKD)
- if you have diabetes.

Drinking enough water
Tolvaptan Accord causes water loss because it increases your urine production. This water loss may result in side effects such as dry mouth and thirst or even more severe side effects like kidney problems (see section 4). It is therefore important that you have access to water and that you are able to drink sufficient amounts when you feel thirsty.

Children and adolescents
Tolvaptan Accord is not suitable for children and adolescents (under age 18).

Other medicines and Tolvaptan Accord
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes all medicines obtained without a prescription.

The following medicines may increase the effect of this medicine:
- ketoconazole (against fungal infections),
- macrolide antibiotics,
- diltiazem (treatment for high blood pressure and chest pain),
- other products which increase the salt in your blood or which contain large amounts of salt.

The following medicines may lower the effect of this medicine:
- barbiturates (used to treat epilepsy/seizures and some sleep disorders),
- rifampicin (against tuberculosis).
- St. John's wort, a herbal medicinal product used to treat depression.

This medicine may increase the effect of the following medicines:
- digoxin (used for treatment of irregularities of heartbeat and heart failure),
- dabigatran etexilate (used to thin the blood),
- metformin (used to treat diabetes),
- sulfasalazine (used to treat inflammatory bowel disease or rheumatoid arthritis).

This medicine may lower the effect of the following medicines:
- desmopressin (used to increase blood clotting factors).

It may still be alright for you to take these medicines and Tolvaptan Accord together. Your doctor will be able to decide what is suitable for you.

Tolvaptan Accord with food and drink
Avoid drinking grapefruit juice when taking Tolvaptan Accord.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Do not take this medicine if you are pregnant or breast-feeding.

Adequate contraceptive measures must be used during use of this medicine.

Driving and using machines
Tolvaptan Accord is unlikely to adversely affect your ability to drive or to operate machinery. However, you may occasionally feel dizzy or weak or you may faint for a short period.

Tolvaptan Accord contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Tolvaptan Accord

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

- Treatment with Tolvaptan Accord will be initiated in hospital.
- For treatment of your low sodium (hyponatremia), your doctor will start with a dose of 15 mg and may then increase it to a maximum of 60 mg to achieve the desired level of serum sodium. To monitor the effects of Tolvaptan Accord your doctor will do regular blood tests. To achieve the desired level of serum sodium your doctor can give in some instances a lower dose of 7.5 mg.
- Swallow the tablet without chewing, with a glass of water.
- Take the tablets once a day preferably in the morning with or without food.

If you take more Tolvaptan Accord than you should
If you have taken more tablets than your prescribed dose, **drink plenty of water and contact your doctor or your local hospital immediately.** Remember to take the medicine pack with you so that it is clear what you have taken.

If you forget to take Tolvaptan Accord
If you forget to take your medicine, you have to take the dose as soon as you remember on the same day. If you do not take your tablet on one day, take your normal dose on the next day. Do not take a double dose to make up for a forgotten dose.

If you stop taking Tolvaptan Accord
If you stop taking Tolvaptan Accord this may lead to reoccurrence of your low sodium. Therefore, you should only stop taking Tolvaptan Accord if you notice side effects requiring urgent medical attention (see section 4) or if your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice any of the following side effects, you may need urgent medical attention. Stop taking Tolvaptan Accord and immediately contact a doctor or go to the nearest hospital if you:

- find it difficult to urinate
- find a swelling of the face, lips or tongue, itching, generalised rash, or severe wheezing or breathlessness (symptoms of an allergic reaction).

Consult your doctor if symptoms of fatigue, loss of appetite, right upper abdominal discomfort, dark urine or jaundice (yellowing of skin or eyes) occur.

Other side effects

Very common (may affect more than 1 in 10 people)
- feeling sick
- thirst
- rapid rise in level of sodium.

Common (may affect up to 1 in 10 people)
- excessive drinking of water
- water loss
- high levels of sodium, potassium, creatinine, uric acid and blood sugar
- decrease in level of blood sugar
- decreased appetite
- fainting
- headache
- dizziness
- low blood pressure when standing up
- constipation
- diarrhoea
- dry mouth
- patchy bleeding in the skin
- itching
- increased need to urinate, or to urinate more frequently
- tiredness, general weakness
- fever
- general feeling of being unwell
- blood in urine
- raised levels of liver enzymes in the blood
- raised levels of creatinine in the blood.

Uncommon (may affect up to 1 in 100 people)
- sense of taste altered
- kidney problems

Not known (cannot be estimated from the available data)
- allergic reactions (see above)
- liver problems
- acute liver failure (ALF)
- increase in liver enzymes.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tolvaptan Accord

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on each blister after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tolvaptan Accord contains

- The active substance is tolvaptan.
  Each Tolvaptan Accord 7.5 mg tablet contains 7.5 mg tolvaptan.
  Each Tolvaptan Accord 15 mg tablet contains 15 mg tolvaptan.
  Each Tolvaptan Accord 30 mg tablet contains 30 mg tolvaptan.
- The other ingredients are lactose monohydrate, maize starch, microcrystalline cellulose, magnesium stearate, croscarmellose sodium, hydroxypropylcellulose, Indigo carmine aluminium lake (E132)

What Tolvaptan Accord looks like and contents of the pack

Tolvaptan Accord 7.5 mg: Light blue to blue coloured, round, biconvex, uncoated tablets, debossed with "MT" on one side and "18" on other side with approximate dimension of 5.0 mm.
Tolvaptan Accord 15 mg: Light blue to blue coloured, triangle, biconvex, uncoated tablets, debossed with '"MT" on one side and "7" on other side with approximate dimension of 6.7 x 6.3 x 3.3 mm.
Tolvaptan Accord 30 mg: Light blue to blue coloured, round, biconvex, uncoated tablets, debossed with "MT" on one side and "8" on other side with approximate dimension of 8.1 mm.

Tolvaptan Accord 7.5/15/30 mg tablets are available as 7x1, 10x1, 28x1, 30x1 tablet in perforated unit dose PVC/Alu blisters in a carton.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est, 6ª Planta,
08039 Barcelona,
Spain

Manufacturer
Accord Healthcare Polska Sp. z.o.o.
ul.Lutomierska 50,
95-200, Pabianice, Poland

Pharmadox Healthcare Limited
KW20A Kordin Industrial Park,
Paola PLA 3000, Malta

Accord Healthcare B.V.
Winthontlaan 200,
3526 KV Utrecht, Netherlands

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.